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Since treatment decisions may be impacted by desires for childbearing following breast cancer diagnosis, this retrospective study was designed to assess the risk of recurrence and death associated with pregnancy following primary and adjuvant therapy. Many oncologists advise young patients to delay decisions about future pregnancies although the suggested latency varies considerably. This collaborative study benefits from the unique resources maintained by the Kaiser Foundation Research Institute. By record-linkage of breast cancer cases with pregnancy databases, more than 110 women have been identified who had one or more pregnancies after initial breast cancer diagnosis. These files also have identified cases without a subsequent pregnancy history closely matching on age and year of diagnosis, stage of disease and months of survival. As anticipated, medical record review for those without a history of post-treatment pregnancy has led to the identification of additional cases with a positive history of pregnancy that did not result in hospitalization and were, therefore, not identifiable from the computerized records. Although we had to relax of several matching criteria, the most essential factors were maintained: stage of disease at diagnosis and survival time comparable for the case and 4 matching comparison subjects. These matching requirements have necessitated thousands of medical records to be reviewed. A preliminary data file has been provided to the Columbia-based biostatistician to begin analyses while additional comparison cases are identified to meet the goal of four cases without subsequent pregnancy for each case with a positive history.

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Does Subsequent Pregnancy Influence Breast Cancer Survival?
Jeanne Petrek, MD

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DOES SUBSEQUENT PREGNANCY INFLUENCE BREAST CANCER SURVIVAL?

INTRODUCTION:

Among young newly diagnosed breast cancer patients, treatment decisions may be impacted by desires for childbearing. Since many women delay childbearing as they complete their education and start careers, an increasing number of young women are being diagnosed with the disease who have not yet married. Delays in initiating childbearing or extending the size of their families are often complicated for women facing radiation and chemotherapy. Recently, patients have taken a more active role in treatment decision-making and are encouraging more research to assess the effect on survival of pregnancy following breast cancer treatment. (1)

With the longstanding recognition of the hormonal dependency of breast cancer (2), clinicians in the past routinely cautioned against pregnancy after breast cancer. Oncologists feared that the hormonal elevations of pregnancy might stimulate latent foci of carcinoma creating an unnecessary risk of disease recurrence. Estrogen and progesterone receptors of the primary tumor have been studied to assess the effect of hormonal treatment on the risk of recurrence and to estimate tumor responsiveness to hormonal changes associated with pregnancy. (3) Oncologists have also been motivated by research that indicates improved survival among premenopausal breast cancer patients following bilateral oophorectomy. Since adjuvant chemotherapy often results in temporary or permanent loss of regular menstrual cycles, its biologic action appears to impact endogenous hormone levels. (4)

Recent modifications in adjuvant protocols to less toxic chemotherapy of shorter duration has enabled more women to retain or regain their menstrual cycles. (5) Some studies have shown regular menstrual cycles have been reestablished with a return of fertility years after completion of treatment. (6) Concern about the safety of pregnancy after primary and adjuvant breast cancer treatment has received more attention during the last few years as patient advocates demand studies that impact their quality of life. (7)

The suggested latency between completion of breast cancer treatment and pregnancy varies considerably among physicians surveyed from six months to ten years. However, the potential hormonal stimulation of pregnancy may not influence the natural history of breast cancer in a homogeneous manner. (8,9) Multiple factors have been associated with breast cancer prognosis including: age at diagnosis, stage of disease, estrogen and progesterone receptor status, type and duration of adjuvant chemotherapy and hormonal therapy, as well as recency of last pregnancy.

The emphasis on early detection of breast cancer has encouraged more young patients to be diagnosed with Stage I disease. In addition, the recommended short course of less toxic chemotherapy has extended disease free survival for young patients. Therefore, young patients are now focusing on the quality of their lives after diagnosis which for many women includes the desire for childbearing. (10) Physicians remain concerned about the effect on prognosis; however, they also recognize the psychosocial needs of their younger patients.

BODY:

Overview of Scope of Work

Data linked through medical records maintained by the Kaiser Permanente Medical Care Program (KPMCP) facilities in Northern California has enabled this collaborative retrospective study in which breast cancer cases diagnosed before the age of 45 have been identified and abstracted to assess survival differences in relation to post-treatment pregnancy history..

The work scope of the project has included:
1. Linkage of the case records with birth records to identify women who have had one or more pregnancies after breast cancer diagnosis. Dates of diagnosis and pregnancy outcome were compared in order to eliminate women who were pregnant at the time of diagnosis of breast cancer. These concurrently pregnant cases are the focus of a separate prognostic study.

2. Matching each case with a positive history of subsequent pregnancy to four breast cancer patients without a history of subsequent pregnancy. Some flexibility on the number of years difference in age at diagnosis and year of diagnosis was needed to identify 4 controls for each case. Matching criteria include: age at diagnosis; year of diagnosis; stage at diagnosis; months of survival from diagnosis to first subsequent pregnancy; and disease status during the early trimester of the first subsequent pregnancy.

3. Abstract data from medical records retained in outpatient and inpatient KPMCP facilities using specially designed data collection instrument to obtain demographic and health history information including: prior pregnancy history; family history of breast cancer; stage of breast cancer at diagnosis and primary and adjuvant treatment information.

4. Matched statistical analyses performed to compare the risk of recurrence and death due to breast cancer of women with a positive history of subsequent pregnancy with matched cases who did not have a post-treatment pregnancy. Preliminary analyses have been initiated.

Key Research Accomplishments

The data management staff of Kaiser enabled the identification of breast cancer cases for linkage with pregnancy databases and follow-up records. A total of 114 women have been identified who had one or more pregnancies after initial breast cancer diagnosis. Data abstraction for these cases has been completed. Linkage of the abstracted data with current data files to obtain date of last contact or follow-up has been performed. All data entry has been conducted by the Kaiser staff.

Women negative for subsequent pregnancy were identified by the computer linkage files and subsequent chart review. To date 340 comparison cases have been identified. Careful review of each medical record identified some of the cases with a positive history since interrupted pregnancies, not requiring hospitalization, were not recorded in the Kaiser database. Careful review also enabled an accurate matching with the degree of flexibility required to identify an adequate number of comparison cases. Medical record abstraction has been completed for the 340 comparison cases and these data are being computerized. Record review is continuing to identify an addition 72 comparison cases without a history of pregnancy after breast cancer to reach the matching goal of 4:1.

Data for this research project has been provided by Kaiser Permanente Medical Care Program (KPMCP) of Northern California which has assigned members of their staff to conduct the data collection aspects. Record linkage between data sets is accomplished with a unique life-long medical record number assigned to each member at the time of initial enrollment. Linkage of cases from the following files has enabled the case-case identification and data collection:

1. The Membership Database. Administrative records with information on age, sex, address, membership group, and number of dependents are available from 1976 for all subscribers to KPMCP. This information is updated quarterly.

2. The Kaiser Permanente Regional Cancer Registry. Records of all cancers among health plan members from 1960 through 1993 are in the data file This cancer registry includes the same data as recorded in SEER files for the Bay Area hospitals and the California State Cancer Registry.

3. The Kaiser Permanente Regional Hospitalization Registry. Computerized files provide the date of hospital admission and the ICD code indicating the reason for hospitalization. These files were used to identify pregnancy associated admissions after the date of breast cancer diagnosis. Since subscribers may attend any KPMCP facility, files from all area hospitals have been accessed.

4. The California Automated Mortality Linkage and Information System . All deaths occurring in residents of California since 1960 are included in this data file.

5. Medical Records. Medical record abstracting is providing epidemiologic information, prognostic factors, treatment information, and disease status at follow-up. KPMCP members are not restricted to specific outpatient facilities; therefore, records related to their medical history before and after breast cancer treatment are maintained at more than one site requiring the abstracted to visit several KPMCP facilities to retrieve all necessary data.

Current Status of Research Project

From the inception of the project a member of the Kaiser research staff trained in medical record abstracting has handled all aspects of the project; Dr. Catherine Schaefer, the Principal Investigator of the consortium agreement, is directing these activities. Dr. Senie visited Kaiser on three occasions between October 1998 and September 1999 while in SF for other purposes. During each visit she met

with key members of the Kaiser Division of Research reviewing the current status of the project with Dr. Schaefer and the Project Coordinator, Ms Barbara Anglin. Specific issues regarding individual cases were discussed and decisions about inclusion of problem cases was addressed. Conference calls and e-mail communication as well as faxes maintained biweekly communication.

Given the stringent matching criteria an inadequate number of matching comparison cases could be identified. One of the primary concerns was the year of diagnosis. Our goal had been an interval of 3 years or less between diagnosis of the 4 comparison cases and the case with a positive history of subsequent pregnancy. However, the number of young cases available for inclusion necessitated a lengthening of the acceptable interval to a maximum of eight years. This longer interval pertained to less than 5% of the matched cases.

A preliminary data file of cases with and without subsequent pregnancy history identified through October 1999 was prepared and enabled the initial comparisons presented on the tables below. Since treatment options for young breast cancer patients have been modified thru the years, one of our primary concerns related to matching addressed the year of diagnosis.

Table 1. Number of years between year of diagnosis for cases with subsequent pregnancy and cases without a history of subsequent pregnancy

Interval - Years	Number cases (%)
No Difference	103 (30%)
1 - 3	189 (55%)
4+	52 (15%)

A majority of the cases were diagnosed between 1980 and 1989 as noted on Table 2. Since adjuvant chemotherapy became a standard of care for most young breast cancer patients during this interval, the findings of the study should be relevant to the current population of patients receiving treatment although the nature of the chemotherapy agents may differ.

Table 2. Comparisons of cases with subsequent pregnancy and cases without a history of subsequent pregnancy

Years of Diagnosis	**Cases – with positive history of pregnancy**	**Cases – without history of pregnancy**
1970 - 1979	**23 (25%)**	**69 (20%)**
1980 - 1989	**59 (63%)**	**199 (58%)**
1990 +	**12 (12%)**	**76 (23%)**
# Pregnancies before Breast Cancer	**Cases – with positive history of pregnancy**	**Cases – without history of pregnancy**

None	20 (21%)	68 (20%)
1 - 2	44 (47%)	151 (44%)
3+	30 (32%)	125 (36%)

The preliminary data also revealed a very similar proportion of women with and without pregnancy after breast cancer were nulliparous at the time of diagnosis.

Linkages with the cases included in the study and the California Mortality data files has been completed for all cases included in the preliminary data file by the Kaiser data managers. However, survival analyses have not yet been initiated as the statistical programs are currently being written. A doctoral student in the Columbia School of Public Health Division of Biostatistics, Ruei-Che Liu, has joined Dr. Senie's staff to handle the analyses of the study data under the direction of Professor Daniel Heitjan of Columbia and with the assistance of Dr. Ann Zauber of Memorial Sloan-Kettering.

Linkage of Datafiles

The data file does not include any personal identifying information. The unique KPMCP medical record number has been scrambled before inclusion in the data file for transfer to Columbia for analysis. Members of the Division of Research of KPMCP have retained a file with both the scrambled and actual medical record number in order to identify subjects if questions pertaining to individual cases arise during analysis.

Statistical Considerations

Matched analyses will be conducted to compare survival among cases with and without a history of subsequent pregnancy. Potential prognostic factors, not included as matching variables, such as prior pregnancy history and family history of breast cancer, will be controlled in the analysis. Analyses among cases with a positive history will address prognostic differences by age at diagnosis and age at subsequent pregnancy. If the number of cases with a positive history of subsequent pregnancy permits, the length of the interval between diagnosis and first subsequent pregnancy, pregnancy outcome, and number of post treatment pregnancies will be studied in relation to survival.

Power Calculations

Using an expected number of 95 breast cancer cases with a history of subsequent pregnancy, estimated power was adequate to detect a hazard of death due to breast cancer with power of 0.80 at 0.05 (2-sided) level of significance. Since the number of identified cases exceeds 95, power should be greater to detect a hazard ratio of 1.7 of less. The influence of pregnancy after breast cancer on risk of disease recurrence will also be studied. The number of women found to have had recurrent disease will be greater than the number of deaths due to breast cancer during follow-up. Consequently, the power will be even greater to detect any differences in risk of recurrence, associated with subsequent pregnancy,

than for mortality. Analyses including only the cases with one or more post-treatment pregnancies will assess survival differences in relation to months between diagnosis and first subsequent pregnancy.

Fewer than expect breast cancer cases with subsequent pregnancy carried to term. Therefore, we may be unable to detect significant associations related to complications of pregnancy and/or neonatal abnormalities detectable at birth.

Benefits & Limitations of Using Kaiser Data

This study benefits from the research staff and resources maintained by Kaiser Permanente. The medical record audit has provided information on prior pregnancy history and other recognized breast cancer risk factors, including family history, which may contribute to disease-free and total survival. Prognostic factors that influence breast cancer survival are available for inclusion in Cox proportional hazards survival models including tumor characteristics, especially estrogen and progesterone receptor levels of the primary tumor, which may influence the impact of pregnancy on the course of breast cancer.

Record linkage of tumor registry files and hospitalization records is a cost-efficient method of identifying Kaiser Permanente patients with a history of post treatment pregnancy eliminating any potential biases due to response rates (94). The guidance provided by this carefully designed retrospective study will augment the limited information currently published.

Limitations inherent in the KPMCP Cancer Registry-based retrospective study make the prospective companion study proposed by Dr. Jeanne Petrek a valuable addition. Although Kaiser Permanente records have been shown to be an excellent resource for research providing an efficient use of historical data, an unfortunate factor is the inability to contact patients (many of whom have died) in order to assess personal characteristics that may relate to their interest in pregnancy after breast cancer. Although the proposed study will provide essential survival information enabling informed clinical guidance by physicians caring for young women treated for primary breast cancer, Drs. Senie and Petrek recognize their inability to assess interest in pregnancy after breast cancer among the control patients. Information on menstrual cycle regularity, a surrogate measure for fertility, will be obtained from medical record abstracting. Pregnancy history recorded at the time of breast cancer diagnosis will be added to the study data base; however, no information about the woman's desire for pregnancy after completion of breast cancer treatment will be available.

A potential limitation that will be carefully addressed concerns the few women diagnosed and treated for breast cancer while members of Kaiser who may have moved to more distant locations, including outside the United States, prior to becoming pregnant or after a subsequent pregnancy. We may be able to ascertain their disease status without resorting to extraordinary means. However, the estimated number of breast cancer patients transferring from Kaiser to another carrier after treatment for a malignancy has been estimated at less than 5%.

REPORTABLE OUTCOMES

NONE – Ongoing Research

CONCLUSIONS

Progress to date has been solely based of identification of the cases with and without a history of subsequent pregnancy. The criteria required modification due to the limited number of young breast cancer patients in the Kaiser records were stringent in order to assure comparability in the analyses. Although we had to relax of several matching criteria, the most essential factors were maintained: stage of disease at diagnosis and survival time comparable for the case and 4 matching comparison subjects. These matching requirements have necessitated thousands of medical records to be reviewed. Given the records are maintained at one of many Kaiser facilities, the medical record abstractor needed to travel among the medical clinics. The project has been more time consuming than originally anticipated.

Preliminary statistical results will be prepared for submission in an abstract due in January 2000. Final results and report writing will be completed by September 2000.

RESEARCH TEAM

As noted in the 1998 report, Dr. Jeanne Petrek has been named as Principal Investigator for administrative purposes. However, Dr. Senie remains responsible for the overall activities of the study. The statistical analyses will be conducted at Columbia by a doctoral student in the Columbia School of Public Health Division of Biostatistics, Ruei-Che Liu with the guidance of Professor Daniel Heitjan of Columbia and Dr. Ann Zauber of Memorial Sloan-Kettering.

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